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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/083,590 | 02/27/2002 | Kostas Iatrou | 028722-274 | 1398 |

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EXAMINER

ZARA, JANE J

| ART UNIT | PAPER NUMBER |
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1635

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/083,590

Applicant(s)

IATROU ET AL.

Examiner

Jane Zara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 February 2002.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 23-36 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 23-36 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 2-27-02.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 2-27-02.

Claims 23-36 are pending in the instant application.

Priority

It is noted that this application appears to claim subject matter disclosed in prior Application No. 09/256,694, filed 2-24-99. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26 and 28-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing an immune response to secreted antigenic determinants derived from pathogenic organisms,

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does not reasonably provide enablement for the generation of a vaccine or antibodies to any secreted heterologous (and pathogenically derived) polypeptide and further whereby pathogenic infections are prevented in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to Make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions, vaccines and methods of generating antibodies to any secreted, heterologous polypeptide, including those derived from pathogenic organisms, and methods of preventing pathogenic infections in a mammal comprising the administration of an expression cassette comprising (operably linked and in 5' to 3' direction) an enhancer, a promoter, a signal peptide, a secretion competent polypeptide and a heterologous protein, which protein may be derived from a pathogenic organism.

The state of the prior art and the predictability or unpredictability of the art. Men et al (J. Virology 65: 1400-1407) teach the unpredictability of vaccine development based upon the use of cloned pathogenic polypeptides: "Despite four decades of research effort, a safe and effective vaccine against dengue virus is still not available...the low immunogenicity of E [antigen] constitutes a major obstacle to the development of an effective ... vaccine produced by recombinant DNA technology." (See last paragraph on the right on page 1400- top of page 1401). Men teach the unpredictability of achieving proper molecular conformation of antigens in vivo following protein secretion from cells: "Presumably assumption of the mature conformation of E is required for

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proper display of major protective sites on E... E constructs that were also secreted efficiently did not induce a detectable E antibody response. This suggests that cell surface expression ... was responsible for its enhanced immunogenicity..." (text on bottom left-top right on page 1406). And this phenomenon of suboptimal antigenicity of secreted recombinant polypeptides is not limited to Dengue virus: "There is evidence from studies with the S antigen of *Plasmodium falciparum* that anchoring the secreted plasmodial antigen on the cell membrane increased immunogenicity severalfold.."

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of generating antibodies for any heterologous polypeptides secreted in a mammal using the instantly claimed expression cassettes, nor any prevention of pathogenic infections in any mammal. The specification teaches the in vitro expression and secretion of heterologous proteins using the instantly claimed expression constructs. One skilled in the art would not accept on its face the examples given in the specification of the in vitro secretion of polypeptides as being correlative or representative of the successful generation of antibodies in an organism comprising the administration of the claimed expression cassettes comprising pathogenically derived polypeptides and further whereby treatment or preventive effects are provided in view of the lack of guidance in the specification and known unpredictability associated with the generation of antibodies from secreted

antigenic sources in an organism and further whereby treatment or preventive effects are provided for any pathogenic disease in an organism.

The breadth of the claims and the quantity of experimentation

required. The breadth of the claims is very broad. The claims are drawn to compositions, vaccines and methods of generating antibodies to any secreted, heterologous polypeptide, including those derived from pathogenic organisms, and methods of preventing pathogenic infections in a mammal comprising the administration of an expression cassette comprising (operably linked in 5' to 3' direction) an enhancer, a promoter, a signal peptide, a secretion competent polypeptide and a heterologous protein, which protein may be derived from a pathogenic organism.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of polynucleotide sequences derived from pathogenic organisms that lead to the generation of vaccines or antibodies in a mammal when they are expressed and secreted in that mammal, and further whereby prevention from pathogenicity is obtained. Since the specification fails to provide any particular guidance for the generation of any vaccines or antibodies against pathogenic polypeptides, and further whereby prevention from pathogenicity is provided, and since determination of the factors (e.g. pertaining to determining optimal antigenicity and subsequent prevention from pathogenicity using any secreted pathogenic polypeptide) is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Lawlis et al.

Lawlis et al (USPN 6,130,063) teach compositions comprising an expression cassette comprising (from 5' to 3') an enhancer, a promoter, a signal peptide, a secretion competent polypeptide, and a heterologous protein, which components are fused in frame in the expression cassette (See abstract, col. 1, line 20-col. 4, line 23; col. 5, line 59 –col. 9, line 27; examples 1 and 2 in col. 12, line 26-col. 19, line 25, and claims 1, 6, 8 and 17).

Claims 23, 24 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Ciardelli et al.

Ciardelli et al (USPN 5,837,816) teach compositions comprising an expression cassette comprising (from 5' to 3') an enhancer, a promoter, a signal peptide, a secretion competent polypeptide from GM-CSF, and a heterologous

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protein, which components are fused in frame in the expression cassette (col. 4, lines 17-54; col. 6, line 65-col. 11, line 49).

Claims 23 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Lo et al.

Lo et al (USPN 5,726,044) teach compositions comprising an expression cassette comprising (from 5' to 3') an enhancer, a promoter, a signal peptide, a secretion competent polypeptide and a heterologous protein, which components are fused in frame in the expression cassette (see abstract; col. 3, line 53-col. 5, line 59).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a

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later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23-25, 27 and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawlis, Ciardelli and Lo as applied to claims 23-25 above, and further in view of Men et al.

The claims are drawn to compositions and methods for inducing an immune response in a mammal against a heterologous protein comprising the administration of an expression cassette to a mammal comprising a polynucleotide encoding a promoter, a signal peptide, a secretion competent polypeptide (optionally comprising GM-CSF) and a heterologous protein which is derived from a pathogenic organism.

Lawlis, Ciardelli and Lo are relied upon as cited in the 102 rejections above. These primary references do not teach compositions comprising expression cassettes comprising a heterologous protein that is derived from a pathogenic organism, nor the administration of the expression cassette to a mammal to generate an immune response.

Men et al (J. Virology 65 :1400-1407) teach the administration of expression cassettes comprising polynucleotides encoding a promoter, a signal peptide and a secretion competent, heterologous polypeptide derived from a pathogenic organism to a mammal, whereby the heterologous polypeptides are secreted and an immune response is induced in the mammal (see especially abstract, text on page 1400, 1401 and 1406).

It would have been obvious to one of ordinary skill in the art to insert a heterologous polypeptide or protein derived from a pathogenic organism into the expression cassettes taught by Lawlis, Ciardelli or Lo because the sequences of the polypeptides of many pathogenic organisms have been taught previously, as disclosed by Men, and replacing the heterologous polypeptides in the cassettes taught previously by Lawlis, Ciardelli or Lo with nucleotides encoding pathogenically derived polypeptides involves routine subcloning and the polynucleotide sequences encoding many pathogenic proteins are known and methods for subcloning are well known in the art. One of ordinary skill in the art would have expected that the administration of a cassette comprising a pathogenically derived polypeptide into a mammal leads to an immune response in that organism, as taught by Men (e.g. an immune response may include cellular or humoral responses, including complement activation and cytokine production, but the generation of antibodies to a particular pathogenic antigen is unpredictable (see 112, first paragraph rejection above and see Men et al). One of ordinary skill would have been motivated to administer the expression cassettes taught by Lawlis, Ciardelli or Lo, wherein the heterologous polypeptide comprises a pathogen derived polypeptide, because these cassettes lead to high expression of secreted polypeptides and an immune response elicited often depends on a threshold quantity (e.g. if degradation occurs after secretion from the cells) as well as the antigenicity of the heterologous polypeptide.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,037,150. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to expression cassettes comprising an enhancer, a promoter operably linked to a secretion competent polypeptide (juvenile hormone esterase) linked in frame to a heterologous protein.

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Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

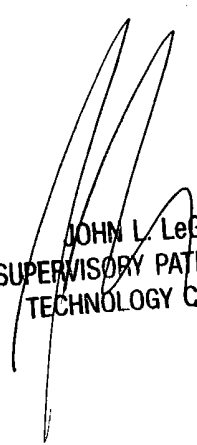
Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760.

Any inquiry regarding

this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

6-22-04



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